Supplemental Materials for Anhedonia and Emotional Experience in Schizophrenia: Neural and Behavioral Indicators

Methods:

Participants: Patients were recruited from local psychiatric hospitals, outpatient settings, and previous studies. Patients were excluded if they had been hospitalized within the past month, or if their medications had not been stable for at least two weeks. Controls were recruited by advertising in local newspapers and posting flyers in the St. Louis, MO, community. All subjects were paid for their participation. All clinical interviews were conducted by a Masters-level clinician who was formally trained on the SCID-IV to a between-rater reliability of 0.8. Inter-rater agreement was routinely assessed and exceeded 0.8 throughout the study using the 22 items of SCID-IV module B (psychosis and associated symptoms).

Example Task Instructions:

Picture Rating Instructions for Valence:

"In this part of the study, I am going to show you some pictures. Some of the pictures will be positive, some will be negative, and some will be neutral. I want you to decide how you personally feel about the pictures, and then to make a response based on how the picture makes you feel. What I want you to do is to press the button with your pointer finger every time you decide a picture is positive. Press the button with your middle finger every time you decide a picture is neutral. Press the button with your ring finger every time you decide a picture is negative."

Picture Rating Instructions for Arousal:

"In this part of the study, I am going to show you some pictures. Some of the pictures will be highly arousing, some will be only a little arousing, and some will not be arousing at all. A picture is highly arousing if it causes you to feel strong emotion about it. That is, you really have strong feelings about what the picture means. A picture is only a little arousing when you feel some emotion about it, but it is not that strong. A picture is not arousing at all when you do not feel any emotion toward the word. Both positive and negative pictures can be highly arousing or only a little arousing. I want you to decide how you personally feel about the pictures, and then to make a response based on how the picture makes you feel. What I want you to do is to press the button with your pointer finger every time you decide a picture is highly arousing. Press the button with your middle finger every time you decide a picture is not arousing at all. Press the button with your ring finger every time you decide a picture is only a little arousing."

Stimuli: Emotional words were taken from the ANEW normed word set (1). Pictures were selected from the International Affective Picture System based on normed valence and arousal ratings (2), and varied with respect to objects, people, locations, and actions. The faces consisted of fearful (negative), happy (positive), and neutral expressions derived from the Ekman (3) and Gur (4) normed face sets. The Gur face set contains mild and extreme intensity emotions that were used for low and high arousal, respectively. For the Ekman faces, morphed images were generated between neutral and emotional expressions for each actor (5), with 50% emotion representing the low arousal condition and 100% emotion representing the high arousal

condition. With the exception of the pictures, all stimuli of equal arousal were matched for valence, and all stimuli of equal valence were matched for arousal. Positive and negative pictures could not be matched for arousal because too few highly arousing images were available for use in the study. The orders of stimulus presentation and of valence versus arousal judgments were counterbalanced across participants.

fMRI acquisition and image analysis: All scans were performed on a 3T Siemens Allegra head-only system. We acquired structural images using a sagittal T1-weighted MP-RAGE sequence [TE = 2.9ms, TR=6.6ms, flip angle=8˚, acquisition matrix=96x128, 80 slices, 2x2.67x2mm voxels]. To facilitate registration of the T1 and functional scans, we also acquired a T2 image in the same space as the functional scans [TE=96ms, TR=5s, 189x256 acquisition matrix, 48 slices, 1.02x1x3mm voxels]. The functional images were collected in runs using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (T2*) [TR=3000ms, TE=25ms, FOV=205mm, flip=90°, 40 axial slices, 3.2mm^3 isotropic voxels]. Stimuli were presented using PsyScope on a G3 Macintosh computer, with each trial onset triggered directly by a pulse from the scanner. A fiber-optic button box interfaced with PsyScope was used to record participants' responses.

The fMRI data was preprocessed and analyzed using in-house software. The functional images were first normalized across runs by scaling whole-brain signal intensity to a fixed value and removing the linear slope on a voxel-by-voxel basis to counteract effects of drift (6). The MR data was then aligned to correct for head motion using rigid-body rotation and translation correction algorithms (7, 8). Frame-to-frame movement and signal-to-noise ratio were compared between groups, and subjects showing excessive movement or poor signal quality were excluded. The structural and functional scans were registered to Talairach Space (9) using a 12 parameter linear (affine) transformation (8), and smoothed with a 6mm FWHM Gaussian filter.

Event-related analyses were used to obtain estimates of activation during the five conditions (NHA, NLA, PHA, PLA, and NEU) for each stimulus type (picture, word, face). For each participant, a general linear model (GLM) (10) was used to estimate a hemodynamic response function for each trial type. The GLM included regressors for linear trends within runs and baseline shifts between runs. An assumed hemodynamic response shape (Boynton function) was used to generate magnitude estimates for each event type, and these magnitude estimates were used in all further statistical analyses.

ROIs: The amygdala and basal ganglia ROIs were derived from manually outlined anatomical templates (11, 12) that were projected into Talairach space, and the dmPFC, rACC, and OFC ROIs were 15mm diameter spherical ROIs centered on the coordinates reported in (13).

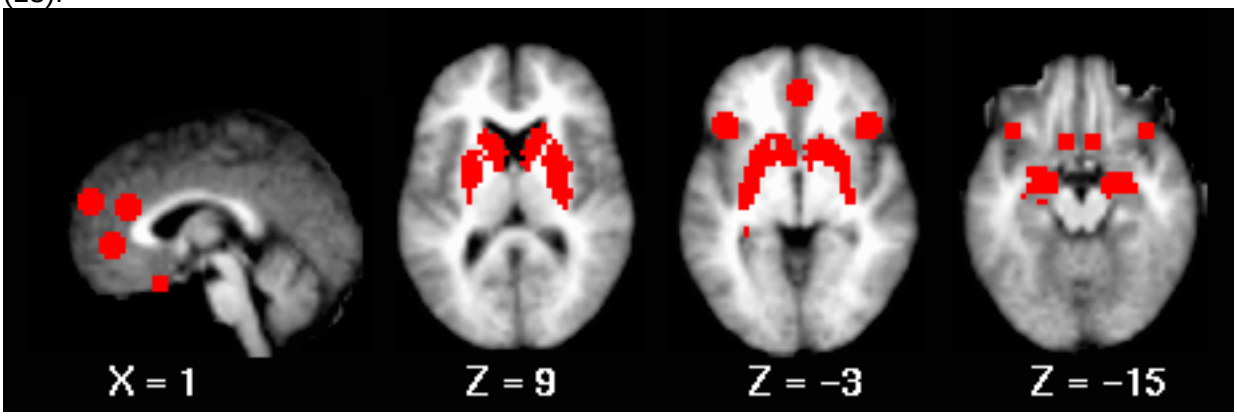


Fig S1

Contrast analyses: To eliminate redundancy, regions identified by both the valence and valenceXarousal contrasts were treated as follows. To determine which contrast better described the activation pattern in such regions, we performed post-hoc pairwise comparisons between the activation magnitudes for each condition. If the region showed both a valence effect (positive <> negative) and an arousal effect (NHA <> NLA or PHA <> PLA), it was evaluated with the valenceXarousal contrast and removed from the valence contrast map. If it showed only a valence effect, it was removed from the valenceXarousal map and evaluated with the valence contrast.

Results:

Movement and signal-to-noise ratio in fMRI data

Three patients and three controls were excluded from analysis for excessive movement and/or low signal-to-noise ratio (SNR). Mean incremental (frame-to-frame) movement was computed for each run for each subject and used to compare movement between groups. For the final sample of 40 patients and 32 controls, mean incremental movement and group t-test results for each translation axis (x, y, z) and rotation axis (pitch, roll, yaw) are summarized in Table S1. The groups differed significantly on movement in the y axis only. SNR was computed by determining the ratio of the mean signal intensity to its standard deviation for each frame within a run, from which the mean, median, and maximum SNR values were determined for each run for each participant. The mean SNR values across runs were then calculated and compared between groups (Table S2). Despite the group difference in y-axis movement, SNR did not differ significantly between groups. Together, these results indicate that the groups were well matched for signal quality and that poor signal quality in patients is unlikely to contribute to the group results reported here.

Table S1: Incremental Movement

	CON		SCZ		
	Mean	SE	Mean	SE	p
x	0.022	0.010	0.046	0.009	0.092
y	0.037	0.005	0.055	0.004	0.010*
z	0.051	0.010	0.077	0.009	0.052
pitch	0.052	0.009	0.072	0.008	0.097
roll	0.025	0.007	0.039	0.006	0.131
yaw	0.021	0.006	0.036	0.006	0.080

SE = Standard Error

Table S2: Signal-to-noise ratio

	CON		SCZ		
	Mean	SE	Mean	SE	p
Mean SNR	340.286	37.116	326.077	33.197	0.776
Median SNR	327.345	19.875	318.206	17.777	0.733
Max SNR	720.273	277.86	789.291	248.53	0.854

SE = Standard Error; SNR = signal-to-noise ratio

Behavioral Valence and Arousal Ratings: effects of stimulus type

Valence and arousal ratings were evaluated with separate repeated measures ANOVAs with stimulus (picture, word, face) and condition (NHA, NLA, NEU, PLA, PHA) as within-subjects factors and group (schizophrenia, control) as a between-subjects factor. For valence (Figure S2a), there was a significant stimulus-by-condition interaction ($F(8, 560) = 12.70$, $p<.001$). There was no main effect of stimulus ($F(2,140) = 0.97$, $p > .37$), interaction of stimulus with group $F(2,140) = 0.77$, $p > .46$), or three way interaction between stimulus, condition and group ($F(8,560) = 0.52$, $p > .74$). Simple effects tests to follow up on the stimulus-by-condition interaction revealed significant effects of condition within each stimulus (faces: $F(5, 350) = 2577$, $p < .001$; pictures: $F(5,350) = 1930$, $p < .001$; words: $F(5,350) = 2739$, $p < .001$), and significant effects of stimulus within each condition (NHA: $F(3,210) = 811.27$, $p < .001$; NLA: $F(3,210) = 1076$, $p < .001$; NEU: $F(3,210) = 3003$, $p < .001$; PLA: $F(3,210) = 3640$, $p < .001$; PHA: $F(3,210) = 3338$, $p < .001$). As shown in figure S2a, within the NHA condition, both groups tended to rate faces as less negative than pictures and words, and in the NLA condition, both groups rated words as more negative than pictures and faces. In the neutral condition, both groups rated faces as more negative than pictures and words. In the positive conditions, both groups rated pictures as less positive than faces and words.

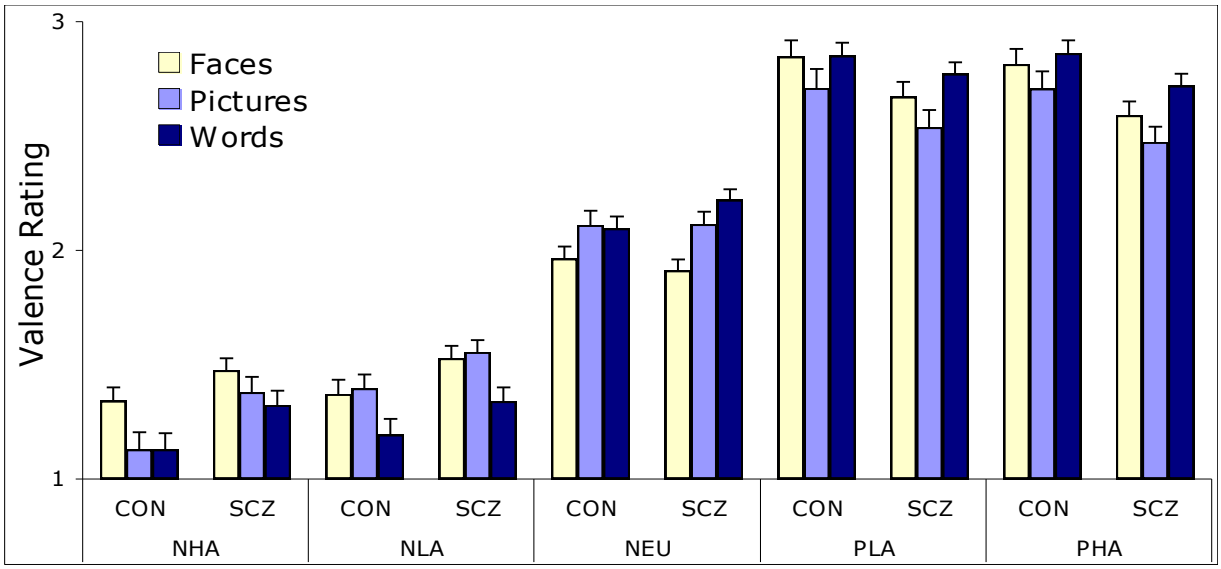


Figure S2a

For the arousal ratings (Figure S2b), there was a significant main effect of stimulus ($F(2, 140) = 23.41$, $p<.001$) and a significant stimulus-by-condition interaction ($F(8, 560) = 5.03$, $p<.001$). There were no significant group-by-stimulus ($F(2,140) =0.36$, $p > .70$) or group-by-condition-by-stimulus ($F(8,560) = 0.76$, $p > .64$) interactions. Overall, words were rated as most arousing, faces were rated as least arousing, and pictures were intermediate. Simple effects tests revealed a significant effect of stimulus within each condition (NHA: $F(3,210) = 517.12$, $p < .001$; NLA: $F(3,210) = 797.53$, $p < .001$; NEU: $F(3,210) = 2427.5$, $p < .001$; PLA: $F(3,210) = 810.03$, $p < .001$; PHA: $F(3,210) = 591.5$, $p < .001$) and a significant effect of condition within each stimulus (faces: $F(5,350) = 1076$, $p < .001$; pictures: $F(5,350) = 872.55$, $p < .001$; words:

F(5,350) = 702.78, p < .001). As shown in figure S2b, in the negative conditions, both groups tended to rate faces as less arousing than pictures or words, and in the positive conditions, both groups tended to rate words as more arousing than pictures and faces. Arousal ratings to neutral stimuli did not differ between stimulus types in either group.

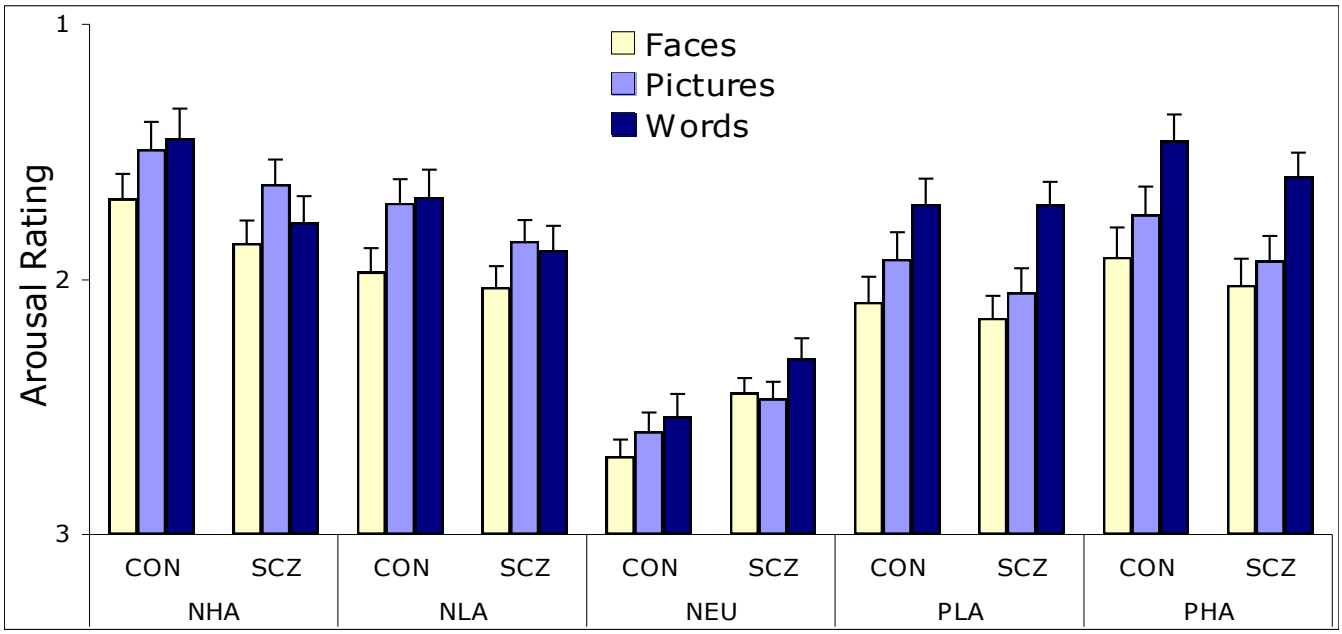


Figure S2b

fMRI analysis: Effects of stimulus type

Table S3 lists regions that showed a significant interaction between stimulus type and each of the three contrasts at the whole-brain level, along with the results of follow-up analyses on the average activity within these regions. The valence and valenceXarousal contrasts identified a similar set of regions, most of which showed within-stimulus effects only for pictures, though a few also showed significant effects for faces. The arousal contrast identified a number of regions driven primarily by pictures, words, or both. As mentioned in the main text, no region was identified that showed a significant stimulusXgroup interaction for any of the contrasts at the whole-brain level. To further probe for an interaction with group, we performed simple effects tests looking for an effect of group within each stimulus type. With one exception, none of these regions showed a significant effect of group within any one stimulus type. Similarly, when we looked for effects of group within each stimulus type, we found that most of the regions showed a significant effect of stimulus type within each group individually.

Table S3: Regions showing a significant effect of stimulus for each contrast:

Brain Region	BA	Talairach Coordinates	# Voxels	*Z*	Stim X Group Interaction	Within-stimulus effects			Within-stim group effects			Within-group stim effects	
						Pictures	Words	Faces	Pictures	Words	Faces	CON	SCZ
Valence Contrast:													
L Cerebellar Declive	-	-30, -57, -15	211	4.92	NS	****	NS	NS	NS	NS	NS	***	****
R Cerebellar Declive	-	33, -52, -11	346	5.16	NS	****	NS	NS	NS	NS	NS	***	****
L Middle Occipital Gyrus	19	-41, -80, 5	313	4.77	NS	****	NS	NS	NS	NS	NS	***	****
R Middle Temporal Gyrus	39	45, -73, 14	139	4.61	NS	****	NS	NS	NS	NS	NS	*	****
R Inferior Frontal Gyrus	9	43, 7, 30	50	3.93	NS	****	NS	****	NS	NS	NS	***	*
L Angular Gyrus	39	-50, -71, 33	37	4.07	NS	NS	*	****	NS	NS	NS	NS	****
R Cuneus	19	29, -85, 31	48	4.50	NS	****	NS	NS	NS	NS	NS	*	****
Arousal Contrast:													
L Middle Temporal Gyrus	39	-52, -64, 11	522	5.63	NS	****	****	NS	NS	NS	NS	****	****
L Inferior Frontal Gyrus	47	-42, 16, -4	116	4.88	NS	***	****	NS	NS	NS	NS	***	****
R Inferior Frontal Gyrus	47	36, 16, -6	38	4.58	NS	***	***	NS	NS	NS	NS	**	***
L Inferior Frontal Gyrus	9	-49, 16, 24	128	4.83	NS	NS	****	NS	NS	NS	NS	*	****
R Middle Occipital Gyrus	19	51, -75, 7	46	4.34	NS	****	NS	*	NS	NS	NS	***	*
L Precuneus	7	-3, -60, 32	295	4.64	NS	****	NS	NS	NS	NS	NS	***	****
L Superior Frontal Gyrus	9	-4, 51, 26	32	4.22	NS	****	NS	NS	NS	NS	NS	NS	****
L Superior Frontal Gyrus	8	-4, 16, 49	358	4.74	NS	**	***	NS	NS	NS	NS	**	****
L Paracentral Lobule	31	-2, -21, 45	47	4.21	NS	****	NS	NS	NS	NS	NS	NS	****
L Middle Frontal Gyrus	6	-32, 3, 59	55	4.11	*	*	***	NS	*	NS	NS	NS	****
Valence X Arousal Contrast:													
L Cerebellar Declive	-	-30, -56, -14	108	4.76	NS	****	NS	NS	NS	NS	NS	***	***
R Fusiform Gyrus	37	36, -55, -11	168	4.93	NS	****	NS	NS	NS	NS	NS	***	****
L Inferior Temporal Gyrus	19	-45, -76, 0	158	4.51	NS	****	NS	NS	NS	NS	NS	****	***
R Middle Temporal Gyrus	39	46, -71, 16	133	4.63	NS	****	NS	NS	NS	NS	NS	*	****
R Inferior Frontal Gyrus	9	43, 8, 31	45	3.89	NS	****	NS	****	NS	NS	NS	***	*
R Cuneus	19	29, -85, 32	42	4.46	NS	****	NS	NS	NS	NS	NS	*	****

*p<.05; **p<.01; ***p<.005; ****p<.001

Whole-brain correlation analyses

Table S4 shows the results of the whole-brain correlation analyses between anhedonia scores and activation in the valence, arousal, and valenceXarousal contrasts. No regions survived the threshold in controls, but several regions were significant in patients.

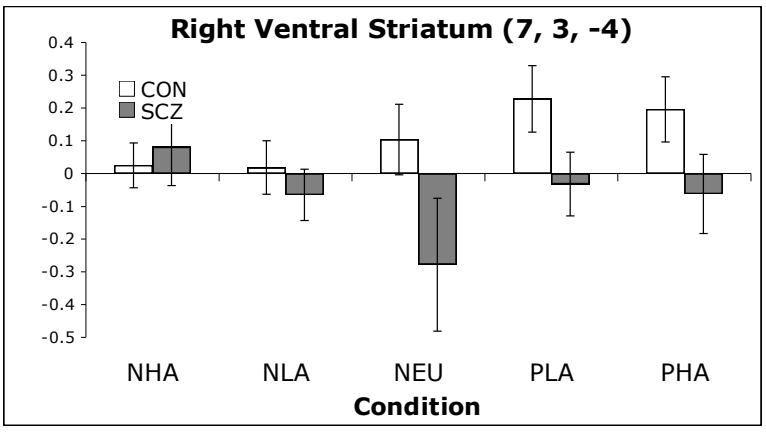
Table S4: Whole-brain correlation results in patients

Contrast	Anhedonia Measure	Talairach Coordinates	Region name	Brodmann Area	# Voxels	*r*	*z*
Arousal	Chapman social anhedonia	-3, 63, 0	L Superior Frontal Gyrus	10	89	0.68	4.81
Valence	Chapman physical anhedonia	-49, 17, -19	L Superior Temporal Gyrus	38	30	-0.56	-3.78
Valence-by-arousal	Chapman physical anhedonia	38, -76, -23	R Cerebellar Tuber	…	50	-0.56	-3.78
		13, -10, -9	R Amygdala	…	45	-0.63	-4.37
Arousal	Chapman physical anhedonia	8, -18, -13	R Midbrain	…	88	0.58	3.90
Valence-by-arousal	SANS global anhedonia	-28, -59, -21	L Cerebellar Culmen	…	59	-0.64	-4.42
		0, 8, -14	Subcallosal Gyrus	25	50	0.52	3.45
		59, -53, -13	R Inferior Temporal Gyrus	20	38	0.59	4.02
Arousal	SANS global anhedonia	-2, 63, 0	L Superior Frontal Gyrus	10	87	0.61	4.17

Medication effects on fMRI data

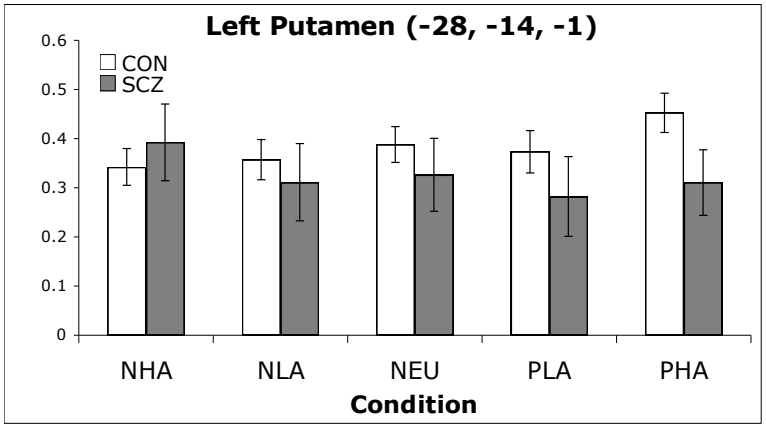
In a sample restricted to the 24 patients who were taking only atypical antipsychotics (excluding risperidone), group t-tests within the two regions that showed group differences in the full sample remained significant. In right ventral striatum (7, 3, -4; figure S3), there were significant group differences in the valence contrast ($t(54) = 2.25$, $p = .03$). The group differences within the positive and neutral conditions dropped to trend-level significance ($F(1,54) = 3.17$, $p = .08$ for NEU, $F(1,54) = 3.25$, $p = .08$ for PLA, $F(1,54) = 2.75$, $p = .10$ for PHA), perhaps reflecting reduced power after exclusion of the 16 patients taking typical antipsychotics or risperidone.

Figure S3



In left putamen (-28, -14, -1; Figure S4), there was a significant group difference in the valenceXarousal contrast ($t(54) = 3.19$, $p = .003$). The group difference in PHA dropped to trend level ($F(1,54) = 3.67$, $p = .06$).

Figure S4



The correlations between physical anhedonia and activation within the right ventral striatum and bilateral amygdala remained significant in the subset of patients taking only atypical antipsychotics. In ventral striatum, physical anhedonia correlated significantly with the valenceXarousal contrast ($r = -.454$, $p = .03$). Physical anhedonia correlated with the valence contrast in left amygdala ($r = -.542$, $p = .006$), and with the valenceXarousal contrast in right amygdala ($r = -.620$, $p = .001$).

When we conducted correlations between antipsychotic dosage in chlorpromazine equivalents and activation in each contrast within the left putamen and right ventral striatal regions, none of the correlations reached significance. We also conducted a voxelwise correlation within our full set of ROIs, and found only one region in the right dorsal caudate that showed a significant correlation in the arousal contrast (coordinates: 16, -14, 21; 23 voxels, $r = .514$, $p < .001$.) This region did not overlap with the regions that showed group differences in activity in the valence and valenceXarousal contrasts.

Schizophrenia versus Schizoaffective Disorder

Our sample included individuals with both schizophrenia and schizoaffective disorder. There has been debate in the literature as to whether or not these represent similar or different disorders. We chose to include individuals with schizoaffective disorder on the basis of a large body of literature suggesting that it is inappropriate to treat schizoaffective disorder as a distinct structural diagnosis. Critical reviews and meta-analyses of the literature in neuropsychology, neuroimaging, molecular neurobiology, and genetic epidemiology have consistently failed to find categorical differences between schizoaffective disorder, schizophrenia, and bipolar disorder, leading several authors to conclude that the current diagnostic structure is somewhat artificial and a dimensional or spectrum approach to psychotic and affective disorders would be more appropriate (14-18). For this reason, we felt it was not necessary to exclude participants with a diagnosis of schizoaffective disorder from our study.

However, to be sure that diagnosis did not have an effect on the data in our sample, we conducted supplemental analyses in which we excluded patients with a diagnosis of schizoaffective disorder from our final sample. The major findings of the study remained unchanged. Behaviorally, the group X condition interactions remained significant for both the valence and arousal ratings, and post-hoc analyses revealed the same group differences within individual conditions as in the full sample. In the fMRI analyses, the group differences in the valence contrast in right ventral striatum and in the valence X arousal contrast in left putamen remained significant, and the negative correlations between physical anhedonia and bilateral amygdala activity remained significant. The negative correlation between right ventral striatal activity in the valenceXarousal contrast and physical anhedonia dropped to trend level (from $r = -.36$, $p < .04$ to $r = -.320$, $p < .08$), possibly due to the reduction in power. We feel that these results show that the diagnosis of schizophrenia vs. schizoaffective disorder did not influence the outcome of our study, and therefore justify inclusion of these patients in our sample.

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